NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

FINAL REPORT - GRANT NGR-33-023-032

"A STUDY OF THE STABILITY OF SLEEP PATTERNS IN YOUNG ADULTS FOR SEQUENTIAL NIGHTS OVER A THREE WEEK PERIOD"

(6-15-68 TO 6-15-70)

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During the period June 15, 1968 to June 15, 1970 the following studies were carried out in our laboratory. These studies were supported in part by funds from NASA Grant # NGR 33023-032.

ACUTE REVERSAL OF THE SLEEP-WAKING CYCLE IN MAN

This study is divided into two major parts. The first was a study of three weeks' duration; first week was a baseline nocturnal sleep period followed by two weeks of an acute 180° inversion to day-sleep. Because of findings of a slow shift of certain physiologic measures a second study lasting for nine weeks was carried out. In this study each subject had a three week baseline nocturnal sleep period, followed by three weeks of sleep during the day, followed by a re-inversion period of three weeks sleeping at night.

The data obtained from these studies are in different stages of completeness of analysis and will be described in this report accordingly.

I. THREE WEEK SLEEP REVERSAL STUDY.

A) Effect on Sleep Stage Patterns (Ref 1)

Method

Five healthy young men lived for three weeks on a metabolic ward. All subjects reported that they normally slept at night and were awake during the day in their prestudy activities. For 7½ days the subjects were allowed to sleep at night for eight hours in an air-conditioned, sound-attenuated, darkened room on a standard hospital bed. Each evening before retiring, standard clinical electroencephalogram electrodes and electrodes for recording the electro-oculogram (EOG) and surface chin electromyogram (EMG) were attached. The electrodes were placed at scalp positions F_3, C_3, and P_3 and referred to both ears, electrically connected ($A_1 + A_2$). One electrode was placed at C_4, to be used if any of the others were faulty during the recording. The EOG was recorded on three channels. The right and left lateral and the

left superior orbital electrodes were referred to the ears ($A_1 + A_2$). Two surface electrodes, taped to the chin, were used in a bipolar arrangement for one channel of EMG, recording. The light was turned off at 10 PM, and the sleep period was then interrupted at 6 AM. During each sleep period for 20 days, EEG, EOG, and EMG were recorded. During alternate sleep periods, an indwelling venous catheter was used to withdraw samples of blood every half hour during sleep for four of the five subjects. This catheter extended ten feet via a small wall aperture to an adjoining room so that blood was obtained without disturbing the subject. In addition, for these subjects blood was obtained by direct venipuncture every four hours on alternate days. Every four hours except for the mid-sleep period, rectal body temperature (oral for one subject) was measured and voided urine obtained for the entire three week period. Analysis of body temperature, plasma, and urine measurements will be described in a subsequent report. During the waking period for the baseline week during the day, and at night after inversion, the subjects had no planned activity. They were instructed not to sleep and were carefully watched by the ward staff. On occasion they were allowed to leave the ward for several hours during their waking time.

A standard diet was served at standard meal times. Food and fluid intake was measured, although the subjects were not obliged to eat or drink the same amount each day.

On the eighth evening, the subject remained awake all night under constant observation and was then allowed to sleep the next morning in the darkened room from 10 AM to 6 PM. Sleep was allowed each day during this eight-hour day period for the next two weeks. All meals, measurements, samples, and recordings proceeded in the previous manner, but at a time 12 hours (180^{o}) out of phase with the baseline first week period. Although there was less activity

and fewer people were on the ward at night, the unit was well staffed at all hours.

The continuous polygraphic records of monopolar EEG, EOG, and EMG recordings were scored in one-minute intervals by experienced technicians, according to the Dement-Kleitman criteria, into awake and sleep stages 1, 2, 3, and 4, and REM (rapid eye movement, sleep). The criteria agree closely with the recent manual for scoring human sleep stages. The scored data for each sleep period was key-punched onto cards and then analyzed statistically with the assistance of digital computer processing.

Results

Shifting the sleep period of the five subjects to a day time interval 180° out of phase with the baseline night sleep period had three effects on the EEG sleep records. (1) The proportion of time spent in certain sleep stages was altered. (2) The hourly distribution of certain stages within the sleep periods changed. (3) The usual sequence of stages was disturbed, and the mean duration of continuous intervals of each stage decreased.

Sleep Stage Amounts.—The duration of each stage within a sleep period for each subject varied from day to day both before and after reversal. Therefore, to describe the trends, mean minutes per sleep period for each stage were averaged for sequential half-week intervals (Table 1). From the first to the second half of the baseline week, there was a significant increase in minutes of stage REM from 104 to 125 minutes, and a significant decrease in stage 2 from 217 to 194 minutes, with little change in the other stages. Changes after reversal were compared with the second half of the baseline week, since the data from the first half week are probably more distorted by the "first night effect" and by other adaptational factors.

Stage Wakefulness (W).—There was a significant increase in wakefulness

immediately after reversal; after reversal the subjects slept less. The duration of waking time was still higher than baseline in the sixth half week, two weeks after reversal. This effect occurred in all five subjects.

Stage 1.—Despite the decrease in duration of total sleep and specific stages, the amount of stage 1 increased after reversal in all four half weeks. This increase was statistically significant ($P < 0.05$) when calculated individually for two subjects but was not significant when determined for the group.

Stages 2, 3, and 4.—There was no significant change in the amount of time spent in these stages following reversal.

Stage REM.—There was significantly less stage REM sleep after reversal. By the sixth half week, two weeks after reversal, the mean duration of stage REM had increased to a level not significantly different from baseline.

Therefore, the effect of reversal on sleep stage amounts was to increase waking time at the expense of REM sleep, with little effect on non-REM sleep stages. This decrease in REM after reversal was associated with a relatively small decrease in the REM percent of total sleep because total sleep also decreased (Table 2).

Hourly Distribution of the Sleep Stages.—During the first week (night sleep prior to reversal), the distribution of the stages throughout the sleep period was highly skewed (Fig 1) as in numerous other studies. Stages 1, 3, 4, and awake were all higher in the first three hours, whereas REM and stage 2 had higher hourly means in the latter part of sleep.

Stage W.—Before reversal, stage W occurred predominantly in the first hour of sleep. After reversal, the amount of stage W decreased significantly in the first hour and increased signficantly in the last three hours. That is, after reversal the subjects fell asleep more quickly, but they tended to awaken

intermittently toward the end of the sleep period.

Stage 2.—After reversal, stage 2 was less concentrated in the latter half of the sleep period.

Stages 3 and 4.—These stages predominated in the first half of the sleep period, both before and after reversal.

Stage REM.—After reversal, the minutes of REM increased during the first half of the sleep period and decreased in the final two hours (Fig 1). The time of sleep onset to the first REM period for all nights of all subjects decreased significantly ($P < 0.05$) during the first postreversal week (week 2) and decreased with borderline significance in the second postreversal week (week 3) ($P < 0.01$), using a t-test for correlated means (Table 3). There was more variability in the latency to the first REM after reversal, and some latencies were extremely short. In the baseline week there were no latencies more than two standard deviations below the mean latency to stage REM onset, while after reversal such extremely small latencies occurred for each subject. One subject, who had no very short REM latencies during the baseline week, developed a pattern of first REM periods occurring essentially at onset of sleep or within a few minutes, and this pattern continued through the second week after reversal.

Thus, during the first week after reversal, there was a clear shift of REM and stage 2 toward the early part of the sleep period, and waking shifted toward the latter part.

Time Sequence of Sleep Stages.—The mean duration of the individual episodes of all sleep stages for the four sequential half-week periods of day sleep were compared to the preceding week of night sleep (Table 4). The duration of episodes of stages REM and 2 decreased significantly in all postreversal periods. Stage 3 decreased in the last three half-week periods, whereas stage 4

decreased significantly only in the latter half of the first week postreversal (week 2). The duration of stages 2 and REM were significantly less for both postreversal weeks. Decreases in the durations of the sleep stage episodes are a measure of the interrupted quality of postreversal sleep. To further define the effect of reversal on REM sleep we defined a REM "epoch" as time from the beginning of a REM period to the end of a sequence of REM periods separated by 15 minutes or less. Both the number of interruptions and the number of interrupted REM epochs increased after sleep-wake cycle inversion (Table 5). Although there was a trend to return to prereversal values, the interruptions were still increased in the second week after reversal.

As a corollary to the above findings, there was an increase in the number of changes of sleep stage after reversal. A mean of 30 changes of stage occurred each night during the baseline week, whereas 37 and 39 were the mean values per night for the second and third week. A selective increase in the number of awakenings from REM periods was also noted following reversal. Prior to reversal, 13% of REM periods were followed by awakenings, whereas after, 29% and 36% of REM periods terminated in awakenings in the second and third weeks.

Because REM interruptions might indicate a disruption in the normal rhythmic cycle of stage REM sleep, we applied a test for rhythmicity of REM occurrences. A binary autocorrelation test, supplied by Gordon Globus, MD, was performed on sleep stage data for each subject for each sleep period. An average result was obtained for the entire group for each of the three weeks. Essentially no difference was found between the mean autocorrelation curves for each of the three weeks when the five subjects were treated as a group. All three curves fell off sharply to minimum agreements at a lag of 45 to 50 minutes and then rose to peak agreements at lags of 90 to 100 minutes (Fig 2).

Individual subjects differed considerably (Fig 2). One subject (S4) had consistently high agreement in the first and third weeks, at a lag of 90 to 110 minutes. During the second week, however, the curves flattened considerably. Subjects S1 and S3 had a consistent 90-minute cycle during week two, whereas this was not consistently present during the first and third weeks. Subjects S2 and S5, on the other hand, had a 90 to 100 minute rhythm during the first week, whereas this was not clearly the case for the second and third week.

Therefore, despite significant changes in duration, amount, stability, and timing of certain sleep stages, the basic 90 to 100 minute cyclicity was preserved following acute inversion to day sleep.

The consistent alteration of sleep pattern after acute inversion of the sleep-waking cycle in these subjects emphasizes the importance of polygraphic definition of sleep stages in studies of circadian cycle shifts. The previous implicit assumptions of a unitary view of sleep can no longer be held in light of the extensive literature documenting the complexity of sleep patterns under a variety of experimental manipulations. Our findings emphasize the differential response of specific sleep stages to an acute inversion of the sleep-wake cycle in a laboratory setting. They demonstrate complex alterations of the phase relations of the sleep stages, the amounts of different stages, and the pattern of sleep stage sequencing.

There was a persistent tendency for spontaneous waking to occur in the latter third of sleep during the inverted sleep period. This was associated with a shift of REM sleep to an earlier time. Further evidence of disturbed REM sleep was shown by the increased frequency of interrupted REM and interruptions of REM sleep epochs. However, the basic 90-minute REM cycle persisted during the day sleep period.

In contradistinction to the disturbances of REM sleep, stages 3 and 4 appeared to shift immediately with the cycle shift. These stages of sleep continued to be present during the first two hours of the sleep period after the 180° shift, as in several previous studies, and suggests that the duration and quality of the waking period may be a factor in determining the timing and amount of stage 3 to 4 sleep. In our study a waking period of 16 hours was always followed upon going to sleep by a similar period of stage 3 to 4 sleep, whether the subject went to sleep at 10 PM or 10 AM.

Although our subjects slept in an equivalent dark room during day and night sleep periods, the light intensity and wavelength spectrum differed while they were awake. In addition, since our subjects were not isolated from the environment during the study period, they were subject to a different social and psychological milieu at night. These factors could have a significant bearing upon the change of sleep patterns.

There is an increasingly important problem of the effects of rapid sleep-wake cycle shift entailed by industrial work shifts and geographical time zone shifts. Alterations in psychological function, work efficiency, and somatic symptoms accompany rapid sleep-wake phase shifts. Our findings of a significant delay in the reestablishment of normal sleep patterns indicate the possible importance of correlating sleep-stage changes to specific occupational work-rest cycle changes. Monitoring sleep patterns and other physiological variables with cycle shift experiments may lead to more rational schedules for work-activity patterns. In the field of occupational medicine there is a substantial body of literature indicating health hazards in situations involving repeated reversals of sleep-waking patterns. Delays in physiologic cycle correspondence have been implicated in the disruption after air and

space travel, with symptoms of fatigue, urinary irregularity, appetite changes, and major disruption of sleep-waking patterns. Alterations in adrenal function and water and electrolyte excretion have been found in transmeridian air flights. The list of occupations involved in sleep-waking reversals is long: airplane pilots, maintenance and traffic control personnel, medical interns, residents and nurses, radar operators, truck drivers, taxicab drivers, postal employees, police and fire department workers. As man works increasingly in situations without regard to a repetitive sleep-waking cycle, the disruption of physiologic circadian rhythms affects mental and physical health, especially if complicated by environmental isolation or mental and physical stress.

B) Effect of Acute Sleep-Wake Reversal on Body Temperature, Urinary Electrolytes, Creatinine, 17-Hydroxycorticosteroid (17-OHCS) and Plasma Cortisol.

In the same group of subjects, during alternate sleep periods (10 of the 20) an indwelling venous catheter was used to withdraw samples of blood at frequent intervals during sleep. A ten foot long catheter enabled us to obtain these samples in the adjoining room. In addition on the day of venous catheterization, blood was obtained by direct venipuncture every four hours during the non-sleep sixteen hours. The centrifuged and frozen plasma was analyzed for cortisol and growth hormone for three subjects. Every four hours during the entire three week period with the exception of the mid four hour sleep time, rectal body temperature was measured and voided urine obtained. Urine volume, 17-OHCS, Na, K and creatinine were measured for each sample.

The results of the changes of body temperature, urine volume, creatinine, Na, K and 17-OHCS are shown in graph 3. Neither the urinary 17-OHCS nor the body

temperature circadian cycle had fully inverted during the two week day-sleep period. The body temperature curve actually became diphasic, with a drop of temperature occurring both during the new day-sleep period, as well as during the time at night when sleep had previously taken place. The urine creatinine and volume, however, did reverse rapidly, although less creatinine and more urine was excreted during the inverted sleep-wake period.

Since it was especially important to determine the time sequence pattern of change of the above measured variables during the two weeks after sleep inversion, we obtained least squares cosine fitting analyses through the kind collaboration of Dr. Franz Halberg, Chronobiology Laboratories, Department of Pathology, University of Minnesota Medical School. Using their method of "pergressive microscope profile" display, we were able to plot an estimate of the amplitude, phase and time course of these cycle shifts.

In graphs 7 and 8, the rapid shift of the acrophase of both urine volume and creatinine are clearly evident. However, the acrophase did not fully shift 180^{o}, but shifted to approximately 160^{o} - 180^{o} initially and then appeared to delay to approximately 110^{o} - 140^{o}. A composite graph of acrophase values across all five subjects is plotted in graph 5. All urine values shown in this graph except K+ shifted approximately 135^{o} - 145^{o}, whereas K+ which had a different acrophase than the other values shifted only approximately 100^{o}. Graph 6 shows an increasing delay of acrophase of body temperature whereas urinary 17-OHCS had a small advance in phase followed by a progressive delay to approximately 70^{o}.

It is important to emphasize that there was a considerable inter-subject variability. For this reason we feel it important to confirm these findings by the results of the nine week study outlined below.

Measurement of the plasma cortisol levels by half hour sampling during sleep in three of the subjects before and after inversion confirmed the findings in the urine 17-OHCS cycle changes that re-establishment of the nocturnal sleep hormone pattern did not take place during day sleep (Fig 4). In addition, measurement of plasma cortisol every four hours, for the twenty-four hour cycle did not show an inversion of the curve for the first and second week after sleep reversal.

Measurement of plasma growth hormone levels confirmed the previous finding that elevation of this hormone during the first few hours of sleep took place during the inverted day-sleep period (Graph 9).

In summary, therefore a non-geographic inversion of the sleep-wake cycle for two weeks produced a disturbed sleep pattern, different sleep stages being affected differently. Certain physiologic functions appeared to reverse rapidly, whereas others did not fully do so during the two week day-sleep period. Finally two hypothalamic-pituitary hormone systems responded in different ways to the shift. The growth hormone release appeared to shift immediately, whereas the ACTH-adrenal system was not readily inverted.

II. NINE WEEK SLEEP REVERSAL STUDY.

Because of the consistent finding of a significant delay in the reestablishment of a "normal" sleep pattern as well as a concomitant body temperature and adrenal cortical hormone cycle phase shift we have extended the original sleep inversion protocol from three to a total of nine weeks. Each subject sleeps for eight hours at night at a specific time for three weeks. This is followed by a phase shift of 180^{o}, sleeping during the day, again at a specific time for eight hours again for three weeks, and then followed by an 180^{o} re-inversion back to the same baseline night sleep schedule for an additional

three week period. As in the previous protocol EEG, EOG and chin EMG are recorded for each eight hour sleep period (a total of 61 sleep periods for each subject) for definition of sleep stage pattern. Records are scored according to the new Sleep Scoring manual at 1 minute epochs. Electrode placement and recording technique is done according to the recommendations in the manual. As before, body temperature (obtained by a calibrated rectal thermistor probe and recording device), urine volume and a 50 cc urine aliquot is obtained every 4 hours (with the exception of the mid sleep time) throughout the nine week period. In addition, two days each week plasma (5 cc) is obtained by venipuncture every 4 hours, again with the exception of the mid sleep period. The urine sample is analyzed for Na, K, creatinine and 17-OHCS. The plasma is analyzed for cortisol. During the nine week period, the subject is not allowed to sleep at any other time except the eight hour sleep period. A defined diet and fluid intake is maintained with body weight obtained at frequent intervals. The room in which the subject sleeps is acoustically insulated from the environment and is darkened during all sleep periods. The experimental subjects are allowed to communicate freely with the staff and patients on the clinical center, and are given permission to leave the hospital for several hours between data collection times.

All the data obtained from the experiment are punched onto IBM cards, and computer programs have been written and will perform the data analysis.

A total of five subjects have been studied according to the above protocol. Thus far we have scored the sleep stage patterns for four subjects (252 nights). The fifth subject's sleep records are presently being completed. The urine and plasma chemical data are partially completed and are presently

being transferred to IBM cards for data analysis. We, therefore cannot describe results for the above data at the present time. We have analyzed the body temperature curves for all subjects however. The pattern of change in rectal temperature was essentially the same as that found in the three week study. That is a consistent progressive change in the circadian temperature curve following reversal was found across subjects and in both studies. A temperature ($\sim$1.5° F) found during nocturnal sleep was found to occur during day-sleep at the end of the three week inverted time. However, this fall was significantly less ($\sim$.5° F) during the first week after inversion and progressively increased reaching comparable values to the baseline during the third inverted week. In addition, a second fall in body temperature occurred approximately 180° out of phase with the sleep period while the subjects were awake. This drop in temperature progressively lessened until the third week when it was no longer apparent. Thus, an apparent 180° phase shift of the circadian body-temperature cycle took place during the third week of the inverted sleep-wake cycle. However, upon re-inversion of the cycle to the baseline state, the temperature cycle reestablished the pre-inversion curve within a few days (Fig 10). This latter finding is important since it indicates that although apparent inversion had occurred after three weeks, the brain mechanisms were still well established for the original cycle, since re-inversion occurred so rapidly.

III. STUDY OF THE EPISODIC SECRETION OF CORTISOL.

Because of our previous finding of intermittent elevation of plasma levels of cortisol during the latter half of the sleep period we carried out a study to determine whether these blood concentration changes represented a new secretion from the adrenal cortex or whether they represented shifts

of endogenous hormone from tissue pools. We utilized a method using C^{14} labeled cortisol administered intravenously such that any decrease in specific activity would mean new unlabeled cortisol had entered the plasma pool.

A healthy young adult subject received C^{14} labeled cortisol while he was asleep. After 45 minutes the specific activity (c.p.m. per microgram) of the plasma cortisol was measured at frequent intervals by double isotope derivative analysis using carrier addition and recrystallization to constant isotope ratio. Cortisol levels were also measured on separate portions of the same plasma sample by competitive protein binding analysis and by radiochemical techniques using ^{3}H-cortisol to check manipulative loss. A separate comparison of protein binding and radiochemical methods was also made. It was shown that satisfactory agreement was obtained by these methods. It was shown that rises in plasma cortisol were accompanied by drops in cortisol specific activity (c.p.m. per microgram) (Fig 13). Falls in plasma cortisol level were associated with an unchanged specific activity. The results demonstrated that in the early morning hours during sleep cortisol was secreted in episodic bursts which were separated by intervals during which there was no cortisol secretion whatever (Fig 12). Utilizing the competitive protein binding method the plasma cortisol level was measured in another normal man at 20 minute intervals over a 24 hour day. It was shown that cortisol was secreted episodically throughout the sleeping and waking day in 8 periods of activity separated by quiescent periods (Fig 11). In both these men estimates of cortisol production rate were measured by isotope dilution analysis using the urinary metabolites tetrahydrocortisol and tetrahydrocortisone. With some reasonable assumptions it was possible to calculate the approximate amount of cortisol secreted

during the episodic adrenal activity. Summation of these estimates gave values in excellent agreement with the measured production rate. Approximately half the day's cortisol production is achieved in the early morning hours during sleep and the secretory episodes are temporally related to rapid eye movement sleep although the relationship is not episode for episode. There was no evidence for steady-state conditions in cortisol level in any portion of the sleep-wake day. It was estimated that the adrenals were secreting at most only 6 hours in a day and were quiescent for the remaining 18 hours.

It is evident from these results that the previous hypothesis advanced has been fully confirmed, ie., secretion of cortisol was an intermittent process during the night while the subject was asleep with periods when there was no secretion of the hormone whatsoever. The previous postulate that the intermittent release of significant quantities of cortisol during the latter half of a night's sleep is under recurrent CNS control, therefore, continues to be an attractive one. With regard to the cortisol production during the 24 hour day, it is apparent that at no time in 24 hour day did "steady state" conditions exist in the level of plasma cortisol. The plasma cortisol level was characterized by a succession of peaks and troughs. Therefore, emphasis must be given to the frequency of sampling.

From the present data and the curves of plasma cortisol and of plasma ACTH published by other investigators, it is almost certain that the secretory events demonstrated in Fig. 11 are characteristic of most normal subjects with allowances for individual variability. It is important to emphasize that this intermittent activity does not form a smooth curve and that the secretory phases and the resting phases are grossly divergent, with a substantial fraction of the day's secretion generated during sleep. It is appropriate to recognize that at least two major endocrine glands, the pituitary and adrenal, are

therefore "programmed" by the CNS, that the program can be changed, albeit with some difficulty, and that the master plan of endocrine activity is probably in the higher centers of the brain and presumably neuronally initiated. Since the normal daily functions of most individuals are repetitive, it is tempting to speculate that the CNS programming of adrenal secretion is predominantly related to recurrent events in the 24 hour cycle but can be influenced by a variety of factors environmental and emotional. This program is transmitted from the higher centers to the pituitary via the hypothalamus to achieve the cyclic secretory events exhibited by the adrenal cortex. The association of adrenal secretory events with sleep may be part of a general program but the sleep cycle is not the sole determinant of the concurrent adrenal cycle (even though much of the day's cortisol production occurs during sleep). An individual can be reprogrammed by change of his sleep-wake cycle among other factors and it is this program that determines the CNS activities that lead to alterations in pituitary ACTH which in turn are reflected in the plasma cortisol levels. It is of some interest to note that this CNS programming of pituitary-adrenal activity can be obliterated by prolonged corticosteroid therapy. The lengthy time required to reinstitute normal pituitary-adrenal activity after steroid withdrawal suggests that repair of a slowly reversible biochemical defect must occur before the normal program can be restored.

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Table 1.—*Comparison of Minutes of Each Sleep Stage Per Eight-Hour Sleep Period by Sequential Half-Week Intervals*

Sleep Stage	Half Weeks (Min) 1	2		3	4	5	6
W	31	32	Reversal	52*	50	48	44
1	7	10		11	14	11	14
2	217*	194		185	201	196	196
3	75	76		75	65	67	63
4	34	35		28	25	29	22
REM	104*	125		93	91*	104*	119

* Values differ significantly (P <0.05) from values of the second half week, latter half of the baseline week.

Table 2.—*Comparison of Percent of Each Sleep Stage to Total Amount of Sleep Per Eight-Hour Sleep Period by Sequential Half-Week Intervals*

Sleep Stage	Half Weeks 1	2	3	4	5	6
1	2	2	3	3	3	3
2	50	44	46	51	48	47
3	17	17	19	17	16	15
4	8	8	7	7	7	5
REM	24	28	25	23	26	28

Table 3.—*Time of Sleep Onset to the First REM Period**

Week	S_1	S_2	S_3	S_4	S_5
1	76±7	83±29	68±15	67±7	62±27
2	60±7	28±30	56±9	55±22	38±28
3	57±28	5±3	60±11	55±26	41±48

* Mean in min ± standard deviation.

Table 4.—*Comparison of the Mean Duration of the Episodes of the Sleep Stages for the Sequential Half-Week Periods of Day Sleep Compared With the Baseline Week of Night Sleep Periods*

Sleep Stage	Baseline Week (Min)	Half Weeks After Reversal (Min) 3	4	5	6
1	3	3	3	2	3
2	18	14*	16*	15*	14*
3	12	12	11	9*	10*
4	16	15	12*	13	17
REM	23	16*	14*	18*	15*

* Significant difference at P<0.01 (t-test).

Table 5.—*Number of Interrupted REM Epochs* and Interruptions of REM Epochs**

Week	S_1	S_2	S_3	S_4	S_5
Interrupted					
1	2	5	4	1	3
Reversal					
2	9	17	12	4	5
3	3	15	11	2	4
Interruptions					
1	2	6	4	1	3
Reversal					
2	12	28	13	5	10
3	3	23	16	2	6

* REM epoch is defined as sequential REM period(s) with interruptions ≦ 15 minutes.

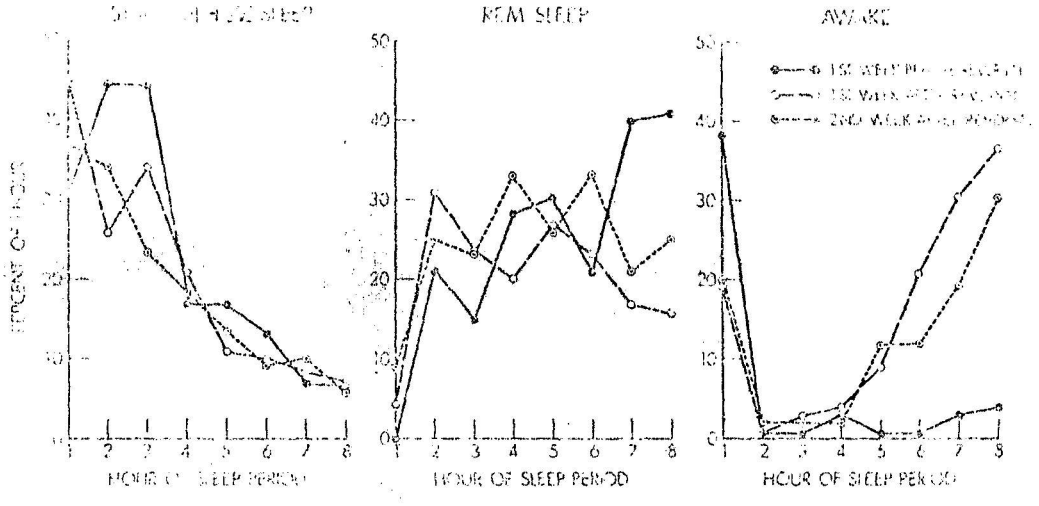
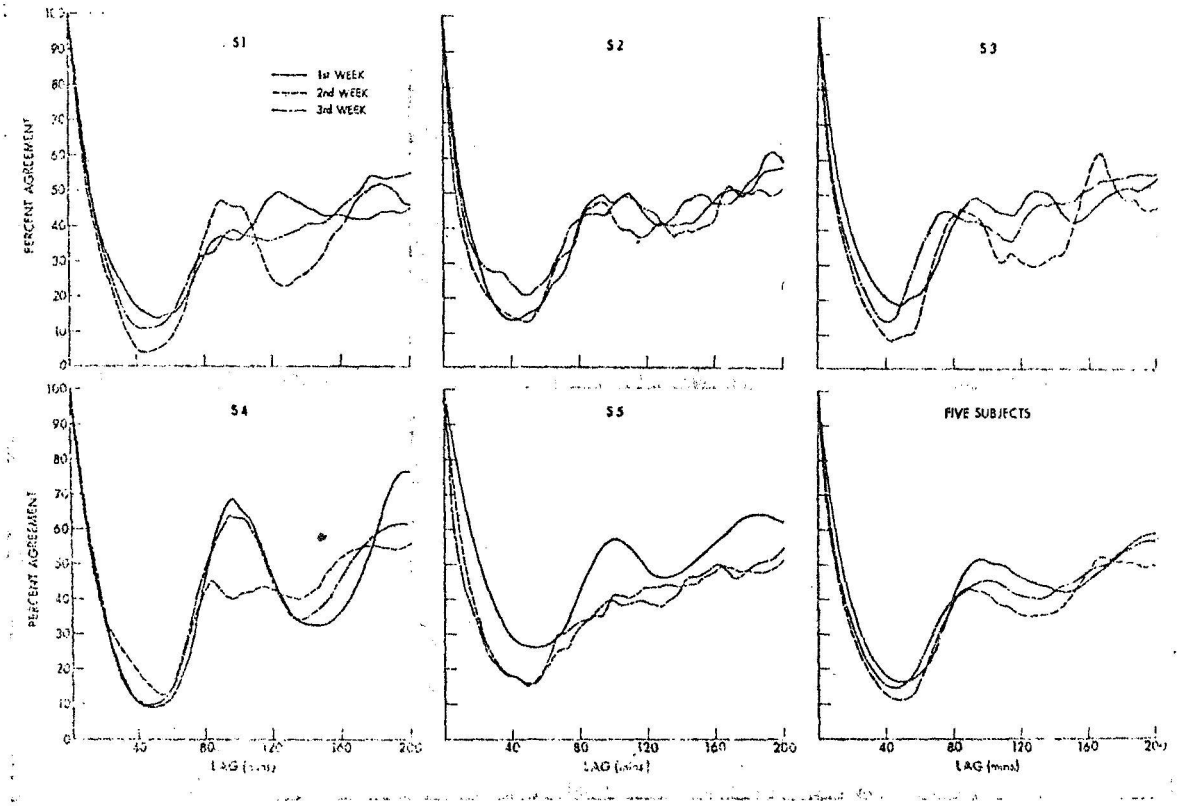


Fig 1.—Mean percent of sleep stages and awake for each hour of sleep period before and after sleep waking reversal.

Fig 2.—Results of a binary autocorrelation test comparing percent agreement with lag time for each of five subjects and for group of five subjects as whole. Uninterrupted line represents values for first week prior to reversal; dashed line, first week after reversal; dash-dot line, second week after reversal.



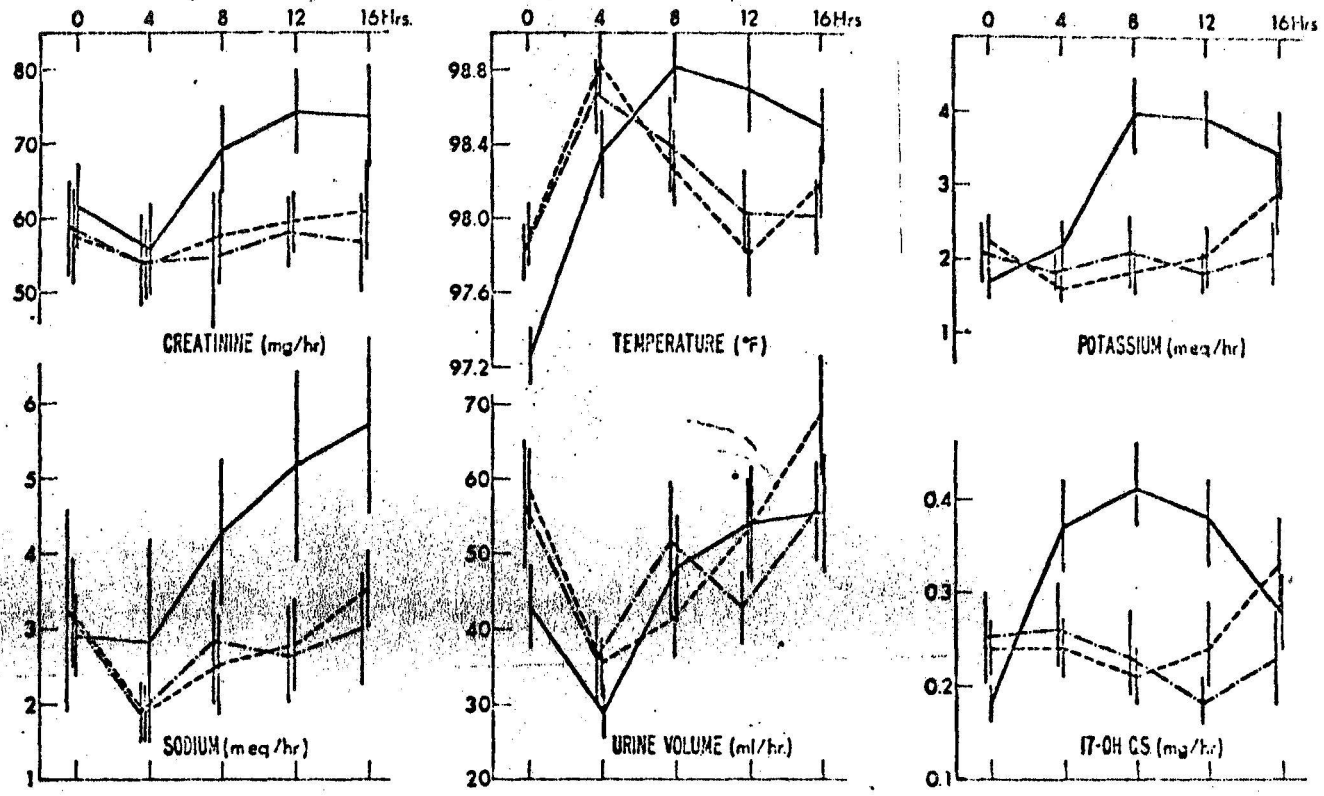


Fig. 3 - Mean and standard deviation of variable graphed a number of hours elapsed after time of awakening. The solid line represents the values for the 1st week (baseline) prior to reversal (sleep time 10 p.m.-6 a.m.), the dashed line, the 1st week after reversal (sleep time 10 a.m.-6 p.m.), and the dash-dot line the 2nd week after reversal (sleep time 10 a.m.-6 p.m.).

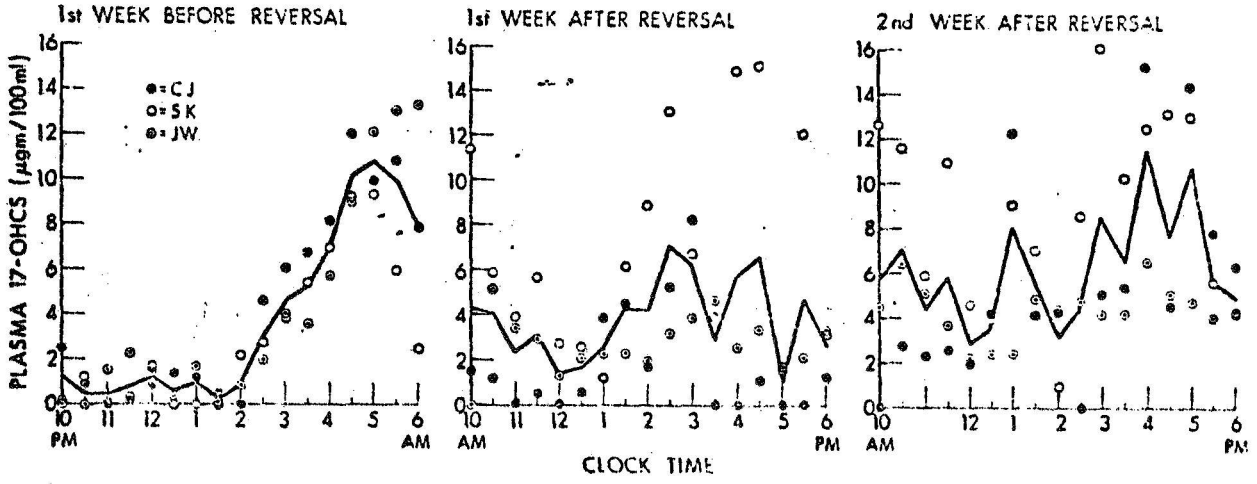
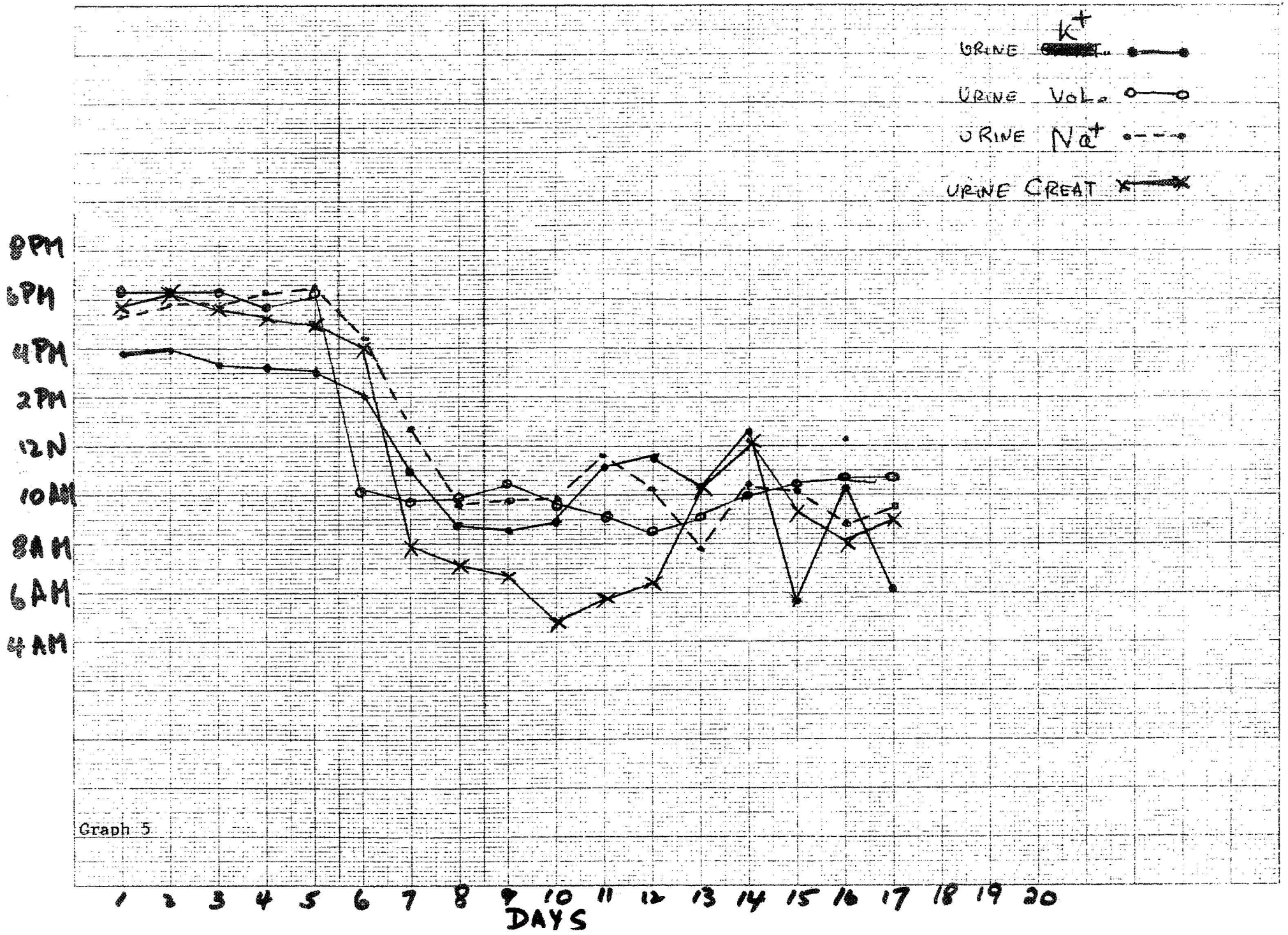
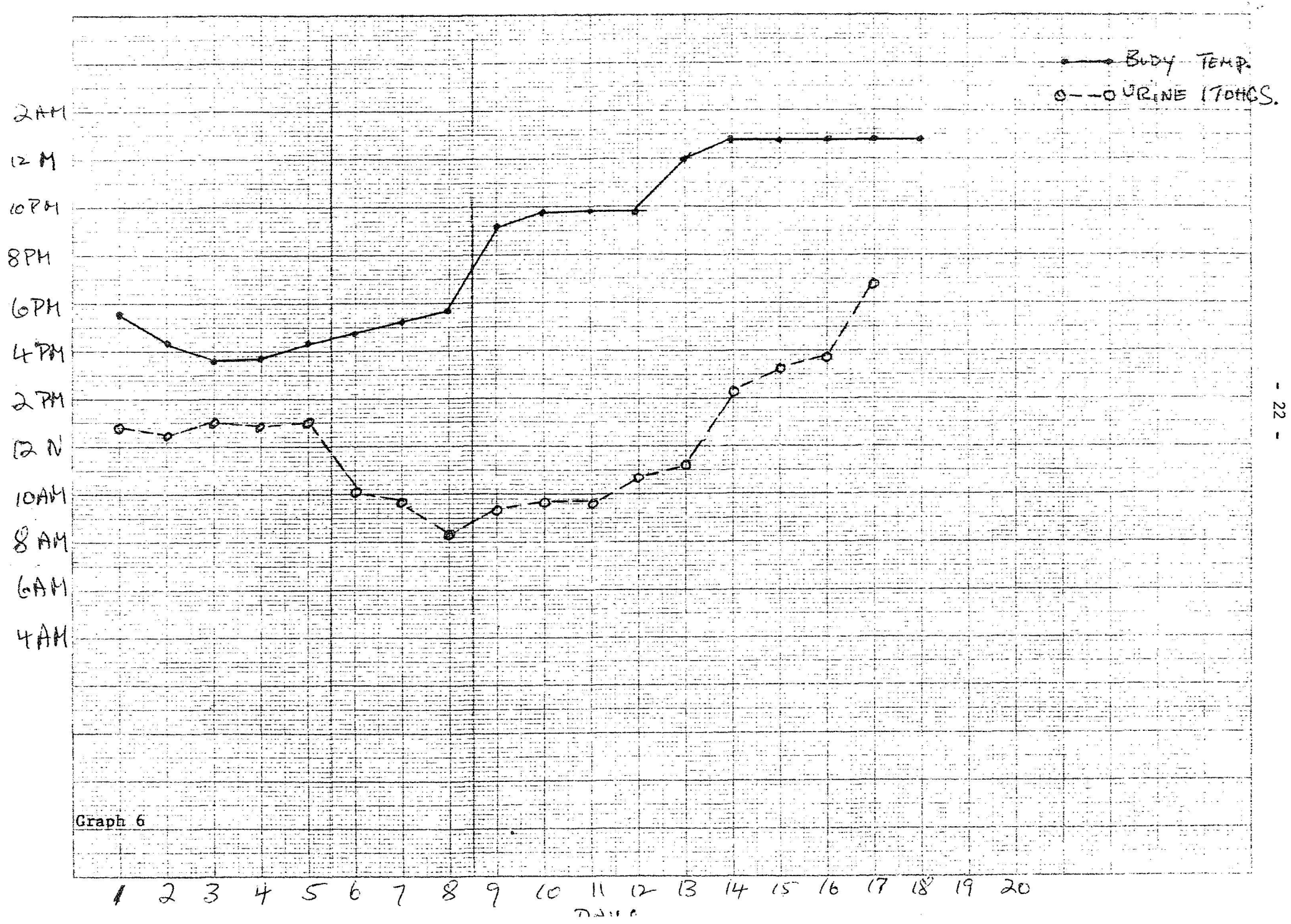


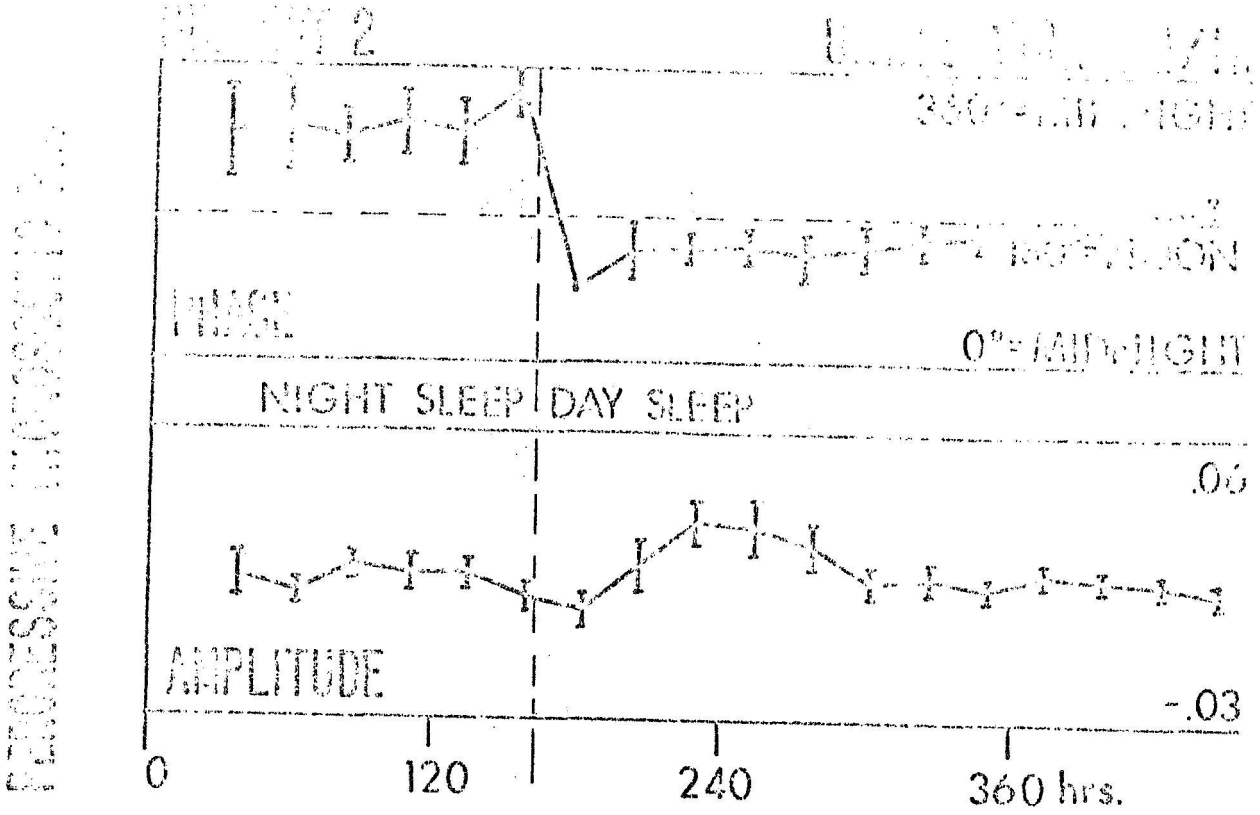
Fig. 4 - Mean levels of plasma cortisol for 3 subjects (CJ, SK, JW) before and after sleep-wake inversion.



Graph 5

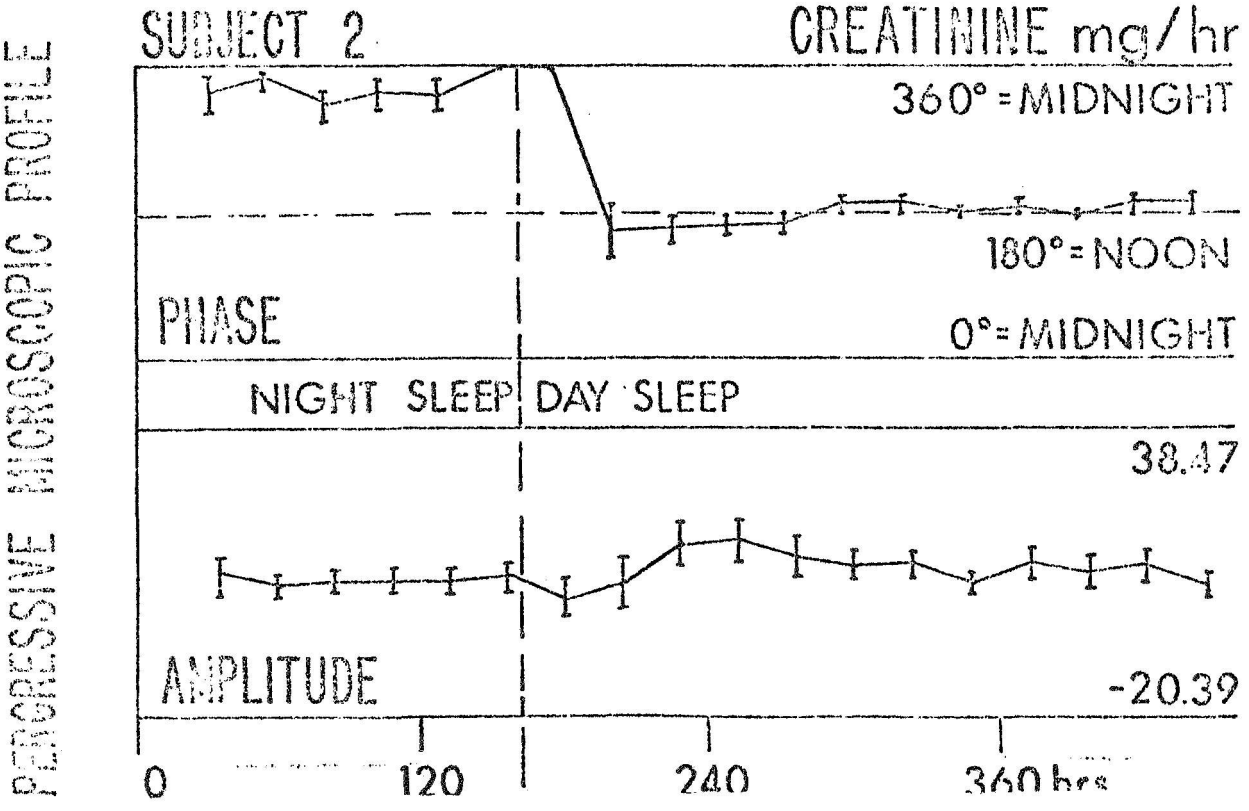


Graph 6



Graph 7

Graph 8



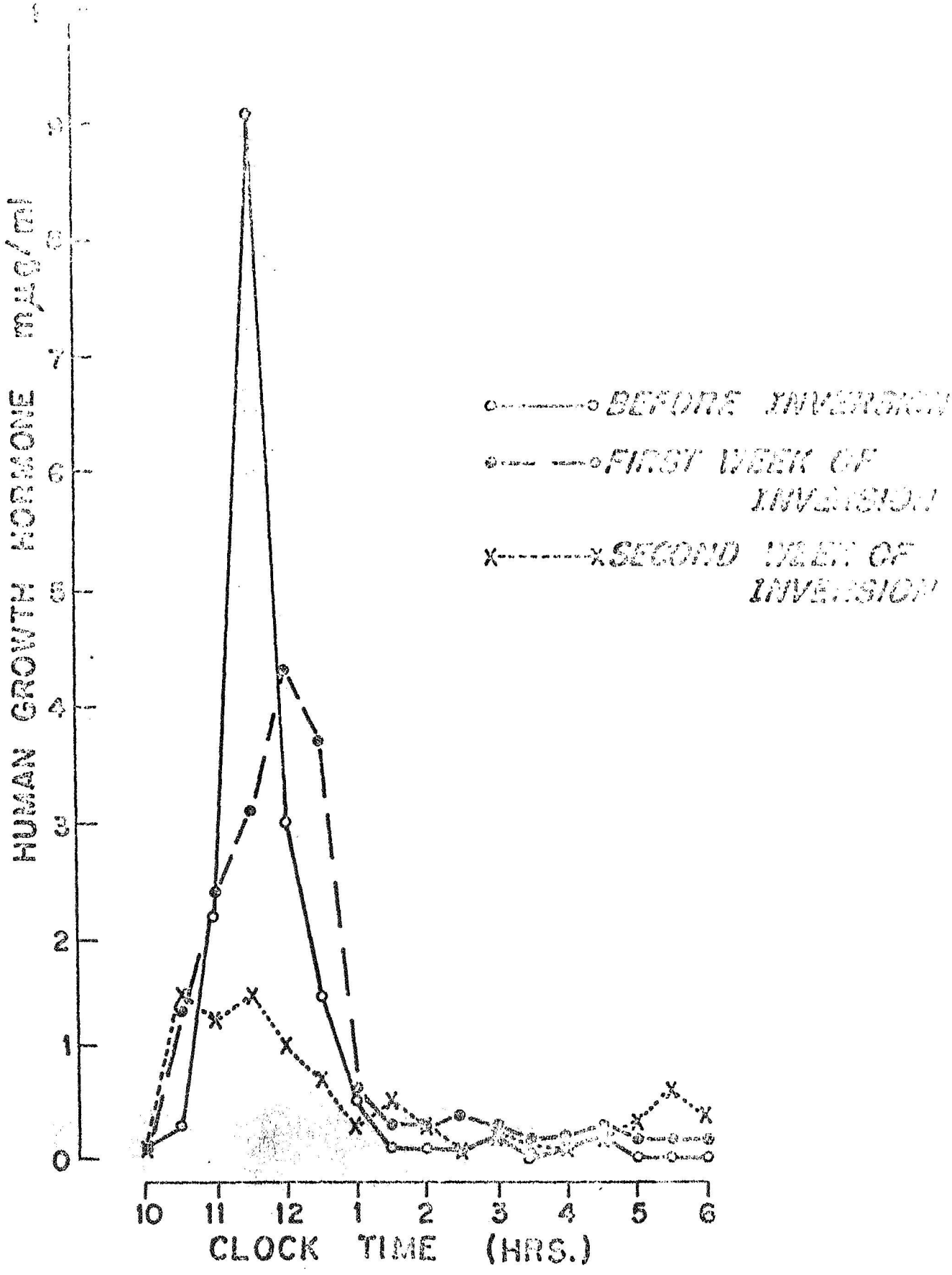

HUMAN GROWTH HORMONE mμg/ml
0
1
2
3
4
5
6
7
8
10
11
12
1
2
3
4
5
6
CLOCK TIME (HRS.)
BEFORE INVERSION
FIRST WEEK OF INVERSION
SECOND WEEK OF INVERSION

Fig. 9

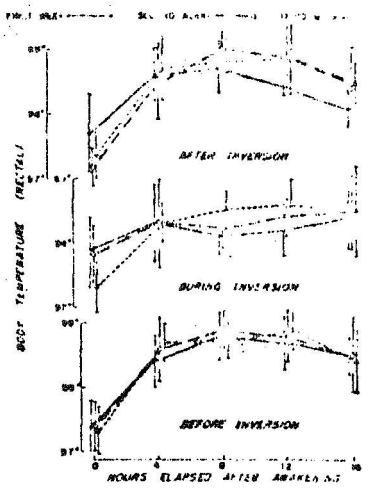

AFTER INVERSION
DURING INVERSION
BEFORE INVERSION

Fig. 10

µg/100 ml
46
42
38
34
30
26
22
18
14
10
6
2
1100
1300
1500
1700
1900
2100
2300
0100
0300
0500
0700
0900
1100
CLOCK TIME
NORMAL

Fig. 11

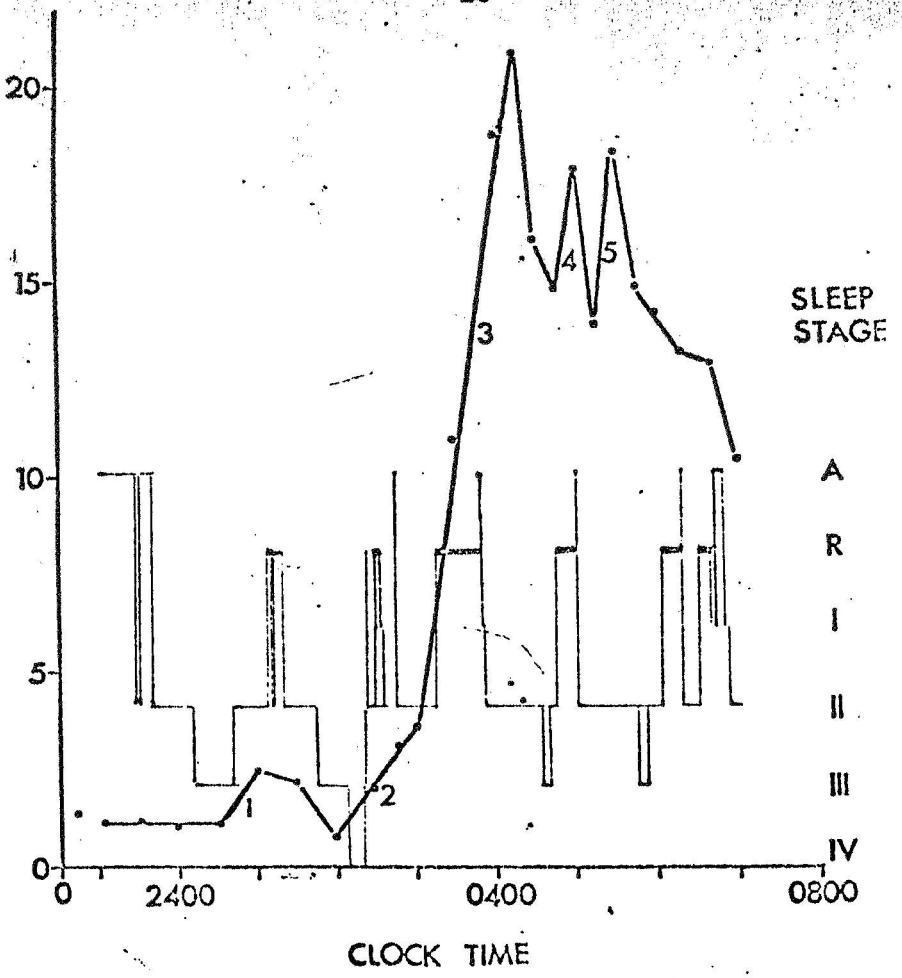


Fig. 12 - Plasma cortisol measurements made every 20 minutes (µg/100 ml) during sleep in a normal young adult.

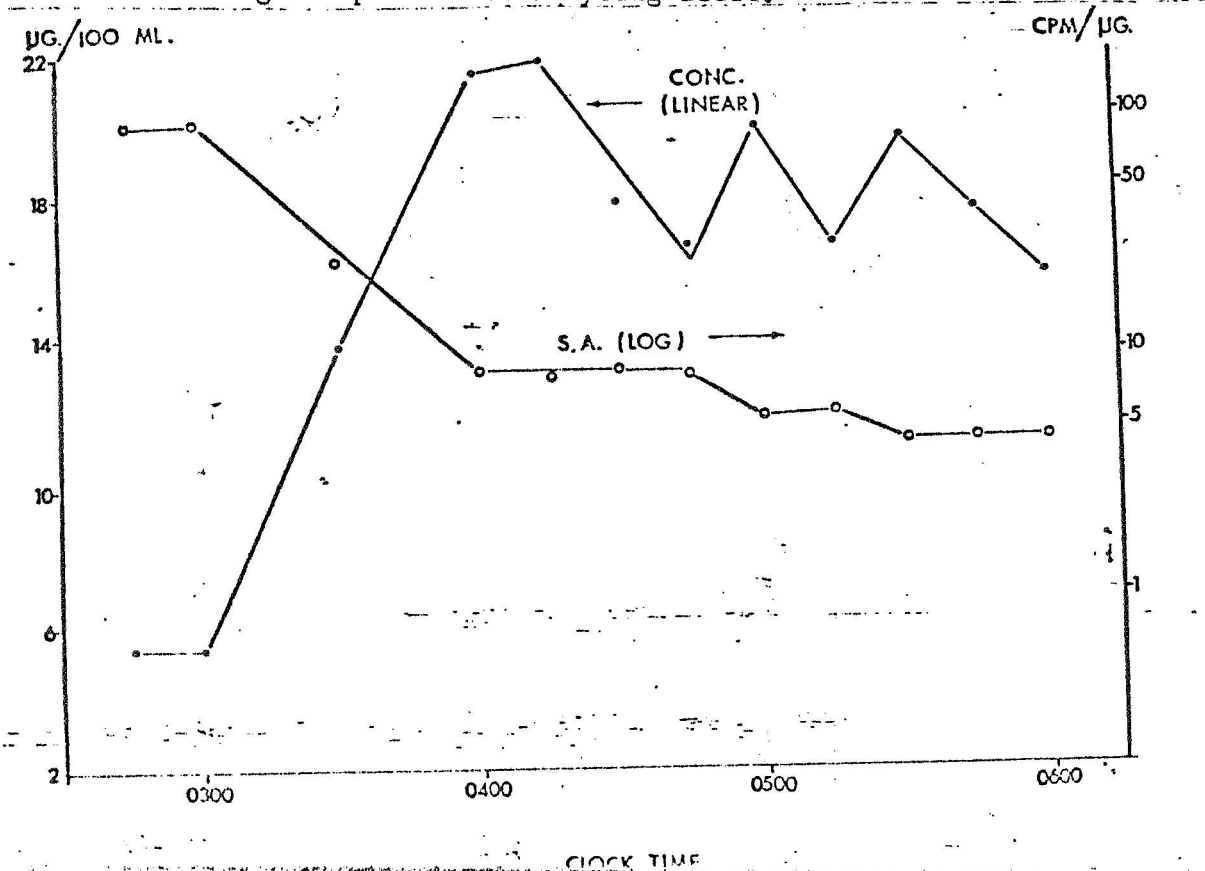


Fig. 13 - Comparison of specific activity of ^{14}C injected cortisol (log scale - cpm/µg) with plasma cortisol levels (µg/100 ml) in sleeping subject shown in Fig. 5.